_®W Inderide® LA

and hydrochlorothiazide) Long-Acting Capsules

(propranolol hydrochloride

No. 455—Each Inderide* LA 80/50 Capsule contains:
Propranolol hydrochloride
(Inderal* LA)

No. 457—Each Inderide* LA 120/50 Capsule contains:
Propranolol hydrochloride
(Inderal* LA)

No. 457—Each Inderide* LA 120/50 Capsule contains:
Propranolol hydrochloride
(Inderal* LA)

No. 459—Each Inderide* LA 160/50 Capsule contains:
Propranolol hydrochloride
(Inderal* LA)

No. 459—Each Inderide* LA 160/50 Capsule contains:
Propranolol hydrochloride
(Inderal* LA)

160 mg
Hydrochlorothiazide

50 mg ${
m R}$ only **DESCRIPTION**Inderide LA is indicated in the once-daily management of hypertension.

hypertension. Indearde LA combines two antihypertensive agents: Inderal (propranolol hydrochloride), a beta-adrenergic receptor-blocking agent, and hydrochloridhizaide, a thiazide diuretic-artihypertensive. Inderide LA is formulated to provide a sustained release of propranolol hydrochloride. Hydrochlorothizaide in Inderide LA exists in a conventional (not sustained-release) formulation. Inderal (prographol hydrochloride) is a synthetic beta-

(not sustaineu-rease) inimiautaini. Inderal (propranolol hydrochloride) is a synthetic beta-adrenergic receptor-blocking agent chemically described as 1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride. Its structural formula is: OH OCH₂CHCH₂NHCH(CH₃)₂ Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.81. Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution; sparingly soluble in methanol; insoluble in ether, chloroform, benzene, and dilute mineral acids. Its chemical name is 6-Chloro-3, 4-dihydro-2H-1, 2, 4-benzothladiazine-7-sulfonamide 1,1-dioxide. Its structural formula is:

Inderide LA contains the following inactive ingredients: calcium carbonate, ethylcellulose, gelatin capsules, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, and D&C Yellow No. 10. In addition, Inderide LA 80/50 mg and 120/50 mg
Capsules contain D&C Red No. 33; Inderide LA 120/50 mg
and 160/50 mg Capsules contain FD&C Blue No. 1 and FD&C Red No. 40. CLINICAL PHARMACOLOGY
Propranolol Hydrochloride (Inderal®)
Inderal is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system
activity. It specifically competes with beta-adrenergic
constructive systems of the precibility agents give

Inderal is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by Inderal, the chrondropic, inortopic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. Inderide LA Capsules (80/50, 120/50, and 160/50 mg) release propranolol hydrochloride at a controlled and predictable rate. Peak propranolol blood levels following dosing with Inderide LA occur at about 6 hours, and the apparent plasma half-life is about 10 hours. Over a 24-hour period, propranolol blood levels are fairly constant for about 12 hours, then decline exponentially. When measured at steady state over a 24-hour period, the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of Inderal Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol. Inderide LA should not be considered a simple mg-for-mg substitute for conventional Inderide Tablets, and the propranolol blood levels achieved do not match (are lower than) those of twice-daily dosing of Inderide Tablets, with the same dose. When changing to Inderide LA from conventional Inderide Tablets, and the propranolol has not been established. Among the factors that may be involved in contributing to the antihypertensive action are: (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympatic necessity and a supplied of the propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although, it readjusts to or below the pretreatment level with chronic usage. Effects on plasma volume appear to be minor and somewhat variable. Inderal has been shown to cause a small increase in serum potassium concentration when used in the treatment of hyperten

concentration when used in the treatment of hypertensive patients. . Beta-receptor blockade is useful in conditions in which, because of pathologic or functional chan

Detarteceptor viockade IS useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate, and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive, which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchoidlator activity, which should be preserved in patients subject to bronchospasm.

The proper objective of beta-blockade therapy is to decrease adverse sympathetic stimulation, but not to the degree that may impair necessary sympathetic support.

Support and may impair necessary sympathetic support.

Hydrochlorothiazide
Hydrochlorothiazide is a benzothiadiazine (thiazide) diuretic closely related to chlorothiazide. The mechanism of the antihypertensive effect of the thiazides is unknown. Thiazides usually do not affect normal blood pressure.

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage, all thiazides are approximately equal in their diuretic efficacy.

Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate.

Onset of diuretic action of thiazide.

bonate.

Onset of diuretic action of thiazides occurs in 2 hours, and the peak effect in about 4 hours. Its action persists for approximately 6 to 12 hours. Thiazides are eliminated rapidly by the kidney. The hydrochlorothiazide in Inderide LA is a conventional (not sustained-release) formulation. INDICATIONS AND USAGE Inderide LA is indicated in the ma hypertension.

This fixed-combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant. CONTRAINDICATIONS Propranolol Hydrochloride (Inderal*)
Propranolol is contraindicated in: 1) cardiogenic shock; ;
sinus bradycardia and greater than first-degree block; 3)
bronchial asthma; 4) congestive heart failure (see
"WARNINGS"), unless the failure is secondary to a tachyarrhythmia treatable with propranolol.

Hydrochlorothiazide
Hydrochlorothiazide is contraindicated in patients w anuria or hypersensitivity to this or other sulfonamic derived drugs. WARNINGS WARNINGS

Propranolol Hydrochloride (Inderal®)

Cardiac Failure: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Heart Failure, continued

talls on neart muscle.

In Patients Without a History of Heart Failure, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or propranolol should be discontinued (gradually, if possible).

old should be discontinued (gradually, if possible).

In Patients With Angina Pectoris, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications. Thyrotoxicosis: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests. In Patients With Wolff-Parkinson-White Syndrome, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

Initial dose of 5 mg propranolol. Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures: cedures.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema): PATIENTS WITH BRONCHOSPASTIC DIS-EASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Inderal should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta recentors.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure in patients on propranolol. Propranolol therapy, particularly in infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting as in preparation for surgery. Hypoglycemia also has been found after this type of drug therapy and prolonged physical exertion and has occured in renal insufficiency, both during dialysis and sporadically, in patients on propranolol. Acute increases in blood pressure have occurred after insulin-induced hypoglycemia in patients on propranolol.

insulin-induced hypoglycemia in patients on propranolol.
Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the drug may develop.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic-blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS General

General Propranolol Hydrochloride (Inderal®) Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol is not indi-

cated for the treatment of hypertensive emergencies Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that propra-nolol may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular

pressure. pressure.

Risk of anaphylactic reaction: While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated chalenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

nephrine used to treat allergic reaction. Hydrochlorothiazide
All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: Hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs irrespective of cause are: Dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. vomiting

Hypokalemia may develop, especially with brisk diuresis when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

use or corrocsserous or Ac-III.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effect of digitalis (e.g., increased ventricular irritability).

Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium

The appearance of these capsules is a registered trademark of Wyeth-Ayerst Laboratories.

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Issued May 8, 2001

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Inderide LA provides propranolol hydrochloride in a susInderide LA provides propranolol hydrochloride in a susInderide Lases form and hydrochloridisacide in conventional formunation, for more-daily administration. In patients are
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hydrochloridisacide) to Inderide LA care any of the backen
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When necessary, another anity perhaps and
mended starting dose, to avoid an excessive fall in blood
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non.
Bradycardia: Administer atropine (0.25 to 1.0 mg). If there
Bradycardia: Administer atropine (actionister isoporoterenol
is no response to vagal blockade, administer isoporoterenol
Cardiac Fallure: Digitalization and diuretics.
Hypotension: Vasopressors, et.g., levarderenol or
Bronchorapasam: Administer isoproterenol and aminophylline.
Bronchorapasam: Administer isoproterenol and aminophylline.

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OVERDOSAGE OR EXAGGERATED RESPONSE
cinospasmi, cardiac failure, hypotension, or bronchospasm. eactions.

Other: Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.
Whenever adverse reactions are moderate or severe, thiransier de dosage should be reduced or therepy withdrawn.

ineadacinis, kalinipusasi, agranulocytosis; thrombocy-Hematologic: Leukopenia; agranulocytosis; thrombocy-cardiovascular. Orthostatic hypotension (may be aggravat-el by alcohol, babilurales, or narcolics). Hypersensibrity; Purpura; photosensibrity; rash; uritearis; nescrioting angilist questinists, utaneora asceutilist; tever; rescrions. "Offiner Hypotellycemia; glycosuria; hyperunicemia; muscile "Offiner Hypotellycemia; glycosuria; hyperunicemia; muscile peagache; xanthopsia. Central Mervous System: Dizziness, vertigo; paresthesias;

liscellaneous: Alopecia, LE-like reactions; psoriasirm rashes; dry eyes; male impotence; and Autoimmune: In extremely rare instances, systemic lupus erythematosus has been reported.

been setablished.

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Clinical studies of Indende LA did not include suffi
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ADVERSE EXECTIONS

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Hydrochlorothiazide

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Pediatric Use

Safety and effectiveness in pediatric patients have not
been established.

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Hydrochlorothiazide

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The antilitypertensive effects of thiszides may be enhanced in the postsympathectomy patient. Thiszides may decrease strents it exponsiveness to norspinelyinne. This diminution is not sufficient to preclude effectiveness of the pressor agent for therspeutic use.

Carcinogenesis, Mudagenesis, Impairment of Fertility combinations of propriatorials, and hydrochlorothiazide have not been evaluated to adversely affect fertility.

redseptive; sinding eclasing vider for in properties of administration of administration of administration of realing sympathetic may produce an excessive reduction of realing sympathetic brackloading, which may result in hypotherision, marked brackloading, vertige, syncopal affacks, or orthostatic hypotherision. ving catecholamine-depleting drugs, such as

Calcium severation is decreased by thiazides. Pathologic Changes in the parathyroid gland with hypercalcemia and phypophoeplasmia have been observed in a few pallents on prolonged thiazide therapy. The common complications of hyperpresentlyroidisms, uch as reast lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function. Thiszides may decrease serum PBI levels without signs of thyroid disturbance.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Ayerst Laboratories Wyeth-Ayerst Company Philadelphia, Pt 19101

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Inderide LA provides propranolog inydrochloride in a sus-

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Gastrointestinal Effects: Though usually of short duration,
Mases may require symptomatic freatment.
Abnormalities in BUM and/or Serum Electrolytes: Monition
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portive mesaures, as required individually, to maintain
after function.
Bossures, as required individually, to maintain
after function.
BOSAGEE AND ADMINISTERATION. Stupor or Coma: Administer supportive therapy as clinically warranted.

Treatment
The following measures should be employed:
General: If ingestion is, or may have been, recent, evacuate
gastric contents, laking care to prevent pulmonary aspiration.

Hydrochlorothiaside Gestrointestinas, knorest, gastric irritation, nausea, vomit-ing, camping; diarrihea; constipation; jaundice (intrahepatic cholestainc jaundice); pencrealitis; saladenitis: Peyronie's disasse have been reported raily.

Oculomucoculaneous reactions involving the skin,
Serous membranes, and conjunctives reported for a beta
proprianolo! have not been associated with
proprianolo!

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available.

Hydrochlorothisatide
Studies in which hydrochlorothiazide was orally administrated.
Studies in which hydrochlorothiazide was orally administrated to pregnant mice and rate at doses of up to 3000 and 1000 mig/gg/dgx, respectively, provided no evidence of history in the studies rouse the placental barrier and appear in cord history in pregnant women requires that the anticipated benefit be weighed against possible has anticipated benefit be weighed against possible has an eso of thiazides in pregnant women requires a jai bundier, at the anticipated benefit be weighed significant prosessible as sanctions of the studies and the adverse reactions that have occurred in the adult.

Proprandol hydrochloride (Indera!")
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Proprandol hydrochloride (Indera!")
Wersing Monthers
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Hydrochlorothistide
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Thiazide drugs may increase the responsiveness to tubocu-arine. Hypotension and cardiac arrest have been reported with the concomitant use of propranciol and halopendol. Wydrochiorthiasticale in Thiskide Mydrochiorthiastical arrest the proprancion and pr Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported.

ratients recen reserpine, sho Drug Interactions Propranclodestates Rydrochloride (Inderal®) priate intervals. Periodic determination of serum electrolytes to detect pos-sible electrolyte imbalance should be performed at approнуагоспіоготпіахіае

ease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase. Clinical Laborator Tests

Propramolol Hydrochloride (Inderal®)

Elevasted blood urea levels in patients with severe heart disagnesses elevated serum transaminases alkaline nhorapatases

confent.

Any chloride deficit is generally mild and usually does not equit sepecific treatment, except under extraordinary circumstances (as in liver or renal decease). Dilutional hyponatemia may occur in edematous patients in hot weather; appropriate trains daminate and or stalk except in ried instances when then the proposition, rather weather; appropriate trains any occur in each relation, rather from the proposition of safety cost, in reduction, rather weather; appropriate trains any occur or trains of the certicition; rather than administration and control of the cost of the proposition of the cost of the certicity of the certification of the cost of the cost of the cost of the cost of the certification of the cost of the